The Synthesis of Natural Acetylenic Compounds from *Stereum hirsutum*

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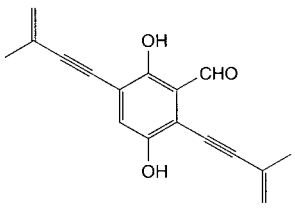
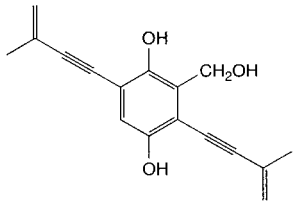
The regioselective synthesis of two new acetylenic compounds, sterehirsutinal (**1**) and sterehirsutinol (**2**), isolated recently from culture medium of the fungus *Stereum hirsutum*, is reported.

Introduction. – *Stereum hirsutum* is a basidiomycete involved in esca, one of the most destructive diseases of grapevine [1]. To find an alternative control method as efficient as the highly toxic sodium-arsenite treatment, the search for a pathogenically active secondary metabolite was necessary. From the culture medium of *Stereum hirsutum*, a series of new acetylenic compounds was isolated [2]. The structure of sterehirsutinal (**1**), and sterehirsutinol (**2**) were elucidated by spectroscopic analysis and by comparison with the biogenetically related frustulosin. Thus, to confirm their structures and to obtain higher quantities of material for bioassays, **1** and **2** were synthetized starting from the commercially available hydroquinone (**3**).



1

Sterehirsutinal



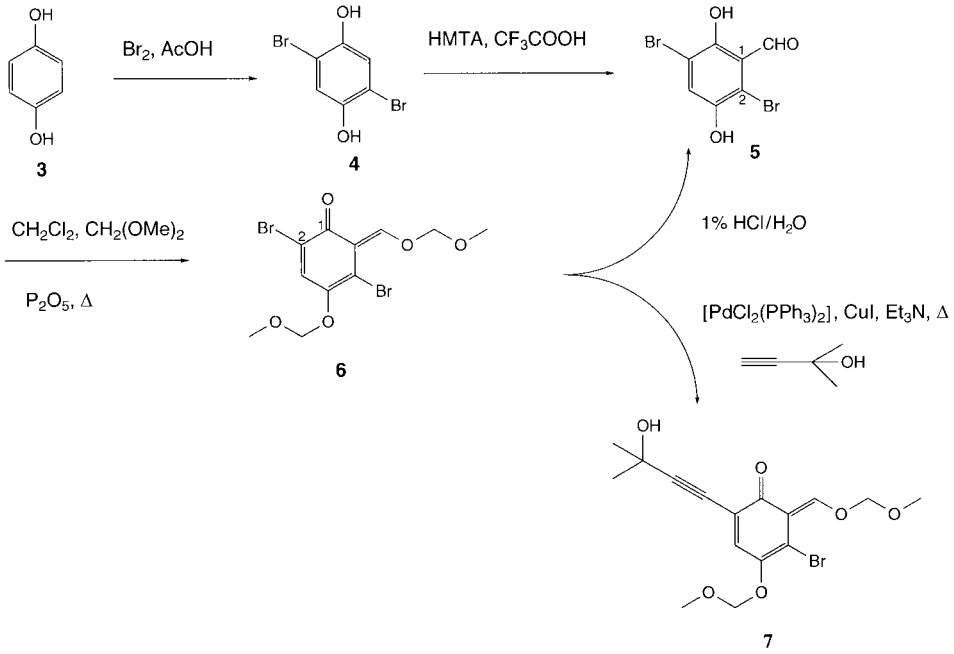
2

Sterehirsutinol

Results and Discussion. – A similar synthetic strategy applied previously for siccayne [3], eutypine [4], and frustulosin [5], compounds containing the same alkenynyl side chain, was followed for the synthesis of **1** and **2**. *retro*-Synthetic analysis suggested that **1** could be prepared by coupling the alkynyl chain with a dihalogenobenzene derivative. The latter compound could be obtained in two steps from hydroquinone (**3**). Thus, the 2,5-dibromobenzene-1,4-diol (**4**) was prepared by bromination of **3** with Br_2 in AcOH (*Scheme 1*). Compound **4** has been prepared previously from benzoquinone in HBr and Br_2 [6], but this method gave a mixture of the mono and dibromo derivatives, which were difficult to separate. The carboxaldehyde function was introduced into **4** by *Duff*'s reaction [7], with hexamethylenetetramine (HMTA) in trifluoroacetic acid ($\rightarrow$ **5**).

To avoid the cyclization reaction leading to a benzofurane derivative [3–5], the phenolic OH groups of **5** had to be protected. Because of the instability of the *ortho*-

Scheme 1

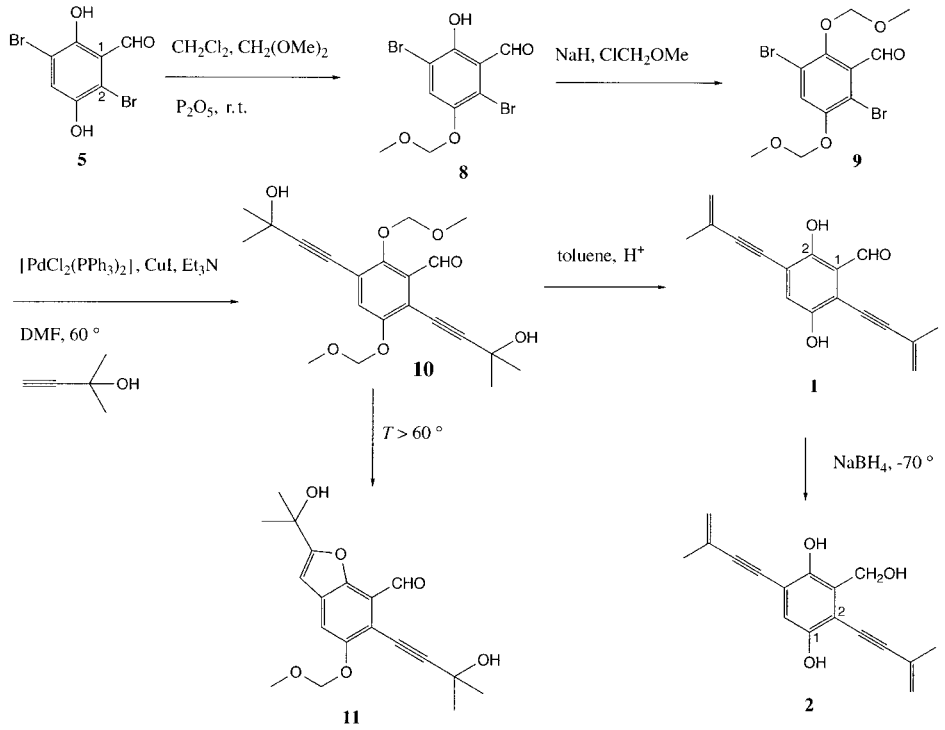


OH acetylenic compounds under acidic conditions, the appropriate OH-protecting group was the methoxymethyl (MOM) group which could be hydrolyzed under mild conditions. Under standard protection conditions (dimethoxymethane and P_2O_5 in CH_2Cl_2 at room temperature), only one of the two phenolic OH groups (OH–C(3)) of **5** reacted to give the mono-protected compound **8** (see below, *Scheme 2*). At higher temperature, a second MOM group was introduced, however, selectively at the aldehyde moiety due to the delocalization of the CH=O bond, to give the enone **6**. Under the same conditions, 2,5-dihydroxybenzaldehyde could be protected at the two phenolic positions. This result suggests that the steric hindrance of the Br-atoms influences the reaction at the aldehyde group; such an unexpected reaction has previously been described for the intramolecular cyclization in the synthesis of heterocycles [8].

Since the enone **6** could be easily hydrolyzed to give back the starting material **5**, we decided to continue the synthesis of **1** and **2** *via* this intermediate. The alkynyl side chain was introduced easily at position 6 of **6** ($\rightarrow$**7**); unfortunately, no alkynylation of **6** occurred at position 3, even at high temperature (90°) (*Scheme 1*). This result forced us to modify the experimental conditions for the protection of the phenolic OH groups of **5**. Thus, **5** was first protected at position 3 in acidic medium to give **8** and then at position 6 in basic medium to give **9** (*Scheme 2*). The dibromobenzaldehyde **9** then underwent the desired coupling reactions with 2-methylbut-3-yn-2-ol in the presence of dichlorobis(triphenylphosphine)palladium ($[PdCl_2(PPh_3)_2]$) and Et_3N in DMF at 60° for 3 h to give the bis(hydroxyalkynyl)benzaldehyde **10**. Temperature and reaction time were crucial in the coupling step. At higher temperature or after more than 3 h at

60°, benzofurancarboxaldehyde **11** was obtained as the major product. The aldehyde group of **10** seems to play the role of catalyst for the deprotection of the adjacent phenolic group, which cyclized to **11**. Finally, the difficult deprotection and dehydration of **10** was accomplished in a one-pot reaction in anhydrous toluene at 60°, in the presence of TsOH and molecular sieves, to give sterehirsutinal (**1**) with moderate yield. Sterehirsutinol (**2**) was obtained in quantitative yield by reduction of **1** with $NaBH_4$ at −70°. Coupling of aldehyde **9** with 2-methylbut-3-yn-2-ol, followed by dehydration of the intermediate **10**, was preferred to the direct coupling of **9** with 2-methylbut-1-en-3-yne, because of the instability and low boiling point of the eneyne [9].

Scheme 2



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Experimental Part

General. All commercially available chemical reagents were used without further purification. CH_2Cl_2 was distilled over CaH_2 and toluene over P_2O_5. M.p.: *Gallenkamp M FB-595-010M*. TLC: Aluminium sheets coated with silica gel *60 F_{254}* (*Merck*). Prep. column chromatography (CC): silica gel (0.063 – 0.200 mm; *60 Merck*). FT-IR: *Perkin-Elmer 1720X*; samples were measured as thin films on NaCl disks, unless otherwise indicated; in cm^{-1}. ^{1}H-NMR: *Bruker AMX 400*; δ in ppm relative to $SiMe_4$ as internal standard, *J* in Hz. MS: electron-impact

ionization (EI) or desorption chemical ionization (DCI); *Nermag-R-30-10* spectrometer. The microanalyses were performed at the Laboratory for Organic Chemistry, ETH Zurich.

2,5-Dibromobenzene-1,4-diol (**4**). A soln. of Br_2 (16 g, 0.1 mol) in AcOH (10 ml) was added dropwise to a soln. of hydroquinone (= benzene-1,4-diol; **3**; 5.5 g, 0.05 mol) in AcOH (40 ml). The mixture was stirred at r.t. for 1 h, H_2O was added, and the brown solid was filtered and crystallized from H_2O: **4** (4.8 g, 36%). White needles. M.p. 190–191°. FT-IR: 3268 (OH), 3094, 3050, 2784, 2076, 1703, 1638, 1515, 1423, 1234, 1222, 1196, 1116, 1061, 863. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.62 (*s*, arom. H); 6.88 (*s*, OH). ^{13}C-NMR ($CDCl_3$): 146.91 (C(1), C(4)); 119.18 (C(3), C(6)); 108.56 (C(2), C(5)). Anal. calc. for $C_6H_4Br_2O_2$: C 26.90, H 1.50, Br 59.65; found: C 26.85, H 1.60, Br 59.92.

2,5-Dibromo-3,6-dihydroxybenzaldehyde (**5**). A mixture of **4** (2.68 g, 0.01 mol), hexamethylenetetramine (= 1,3,5,7-tetraazatricyclo[3.3.1.1^{3,7}]decane; 1.4 g, 0.01 mol) in CF_3COOH (20 ml) was heated under reflux for 16 h. The solvent was evaporated and the residual oil diluted in H_2O (1000 ml) and heated at 60° for 6 h. The mixture was extracted with AcOEt (5 × 100 ml), the org. layer washed with sat. NaCl soln. (10 × 100 ml), dried ($MgSO_4$), and evaporated, and the residual brown oil crystallized from AcOEt/hexane: **5** (2.3 g, 78%). Yellow solid. FT-IR: 3456, 3067, 2922, 2855, 1646, 1437, 1261, 1233, 1181, 1143, 852, 721, 560, 506, 496. ^{1}H-NMR (400 MHz, $CDCl_3$): 12.04 (*s*, OH); 10.16 (*s*, CHO); 7.81 (br. *s*, OH); 7.38 (*s*, arom. H). ^{13}C-NMR ($CDCl_3$): 208.16; 197.07 (CHO); 153.84; 146.58; 127.92 (C(4)); 117.02; 112.21; 110.33. EI-MS: 296 (100, M^+), 266, 39, 07, 187, 157, 131, 88, 73, 70. 61.

2,5-Dibromo-6-hydroxy-3-(methoxymethoxy)benzaldehyde (**8**). To a soln. of **5** (1.5 g, 5 mmol) and $CH_2(OMe)_2$ (excess, 10 ml) in dry CH_2Cl_2 (10 ml), P_2O_5 (3.5 g) was added portionwise. After 2 h, more P_2O_5 (2 g) was added and stirred until **5** disappeared (TLC monitoring). The mixture was diluted with CH_2Cl_2, washed with 1N aq. NaOH and sat. aq. NaCl soln., dried ($MgSO_4$), and evaporated. The yellow solid was purified by CC (AcOEt/hexane 1:9): yellow **8** (1.34 g, 80%). FT-IR: 3443 (OH), 3082, 3002, 2942, 2829, 1650, 1473, 1436, 1417, 1401, 1291, 1272, 1250, 1205, 1161, 1149, 1087, 1017, 942, 919, 879, 822, 760, 733. ^{1}H-NMR ($CDCl_3$): 12.25 (*s*, OH); 10.34 (*s*, CHO); 7.64 (*s*, H–C(4)); 5.16 (*s*, CH_2); 3.53 (*s*, Me). ^{13}C-NMR ($CDCl_3$): 197.55 (CHO); 155.50; 147.10; 129.07 (C(4)); 117.80; 117.04; 110.58; 96.39 (CH_2); 56.64 (Me). DCI-MS: 354 ([M + NH_4]$^+$), 340 (M^+), 310, 275, 185, 157, 133, 88, 73, 70, 61. Anal. calc. for $C_9H_8Br_2O_4$: C 31.80, H 2.37, Br 47.01; found: C 31.96, H 2.48, Br 47.01.

2,5-Dibromo-4-(methoxymethoxy)-6-[(methoxymethoxy)methylene]cyclohexa-2,4-dien-1-one (**6**) was prepared as described for **8**, but at reflux temp. in CH_2Cl_2. Yield: 75%. ^{1}H-NMR ($CDCl_3$): 7.41 (*s*, H–C(3)); 5.40 (*s*, CH); 5.37 (*d*, J = 13.2, 1 H, CH_2OCH=C(6)); 5.33 (*d*, J = 13.2, 1 H, CH_2OCH=C(6)); 5.17 (*d*, J = 6.80, 1 H, CH_2O–C(4)); 5.15 (*d*, J = 6.80, 1 H, CH_2O–C(4)); 3.63 (*s*, Me); 3.52 (*s*, Me). ^{13}C-NMR ($CDCl_3$): 175.93 (CO); 148.45; 145.48; 122.50; 121.65 (C(3)); 112.73; 109.35; 96.01 (CH_2); 95.83 (CH); 84.55 (CH_2); 56.46 (Me); 55.81 (Me). Anal. calc. for $C_{11}H_{12}Br_2O_5$: C 34.40, H 3.15, Br 41.61; found: C 34.40, H 3.21, Br 41.52.

5-Bromo-2-(3-hydroxy-3-methylbut-1-ynyl)-4-(methoxymethoxy)-6-[(methoxymethoxy)methylene]cyclohexa-2,4-dien-1-one (**7**) was prepared as described for **10**. Yield: 81%. FT-IR: 3442, 2981, 2933, 2832, 1739, 1589, 1486, 1458, 1411, 1381, 1350, 1323, 1285, 1245, 1208, 1195, 1155, 1099, 1059, 1031, 998, 961, 881, 813. ^{1}H-NMR ($CDCl_3$): 7.20 (*s*, H–C(3)); 5.37 (*s*, CH); 5.34 (*d*, J = 16.1, 1 H, CH_2OCH=C(6)); 5.29 (*d*, J = 16.1, 1 H, CH_2OCH=C(6)); 5.16 (*d*, J = 9.7, 1 H, CH_2O–C(4)); 5.11 (*d*, J = 9.7, 1 H, CH_2O–C(4)); 3.61 (*s*, Me); 3.51 (*s*, Me); 1.61 (*s*, 2 Me). ^{13}C-NMR ($CDCl_3$): 171.16 (CO); 148.94; 147.73; 121.74; 121.20; 111.15; 99.37; 95.99 (CH); 95.85 (CH_2); 84.24 (CH_2); 65.69; 65.50; 56.40 (Me); 55.70 (Me); 31.33 (2 Me).

2,5-Dibromo-3,6-bis(methoxymethoxy)benzaldehyde (**9**). To a soln. of **8** (1.35 g, 4 mmol) in DMF (20 ml) at 0° under N_2, a 60% NaH suspension in mineral oil (0.21 g, 4.4 mmol) was added portionwise. After 10 min, chloromethyl methyl ether (0.334 ml, 4.4 mmol) was added dropwise and stirred at r.t. for 2 h. The soln. was poured into H_2O and extracted with AcOEt, the org. layer washed with sat. NaCl soln., dried ($MgSO_4$), and evaporated, and the residual yellow oil submitted to CC (silica gel, hexane/AcOEt 95:5): **9** (74%). White solid. FT-IR: 2996, 2963, 2938, 2871, 2834, 1771, 1699, 1660, 1575, 1537, 1485, 1463, 1453, 1438, 1381, 1278, 1237, 1207, 1157, 1090, 996, 939, 920, 887, 868, 827. ^{1}H-NMR ($CDCl_3$): 10.23 (*s*, CHO); 7.56 (*s*, H–C(4)); 5.24 (*s*, CH_2); 5.06 (*s*, CH_2); 3.62 (*s*, Me); 3.51 (*s*, Me). ^{13}C-NMR ($CDCl_3$); 190.02 (CHO); 151.21; 149.86; 131.31; 123.72 (C(4)); 117.78; 113.60; 101.53 (CH_2); 95.64 (CH_2); 58.26 (Me); 56.62 (Me). EI-MS: 384 (68, M^+), 353 (35), 338 (100), 324 (24). Anal. calc. for $C_{11}H_{12}Br_2O_5$: C 34,40, H 3.15, Br 41.61; found: C 34.60, H 3.21, Br 41.44.

2,5-Bis(3-hydroxy-3-methylbut-1-ynyl)-3,6-bis(methoxymethoxy)benzaldehyde (**10**). A soln. of **9** (192 mg, 0.5 mmol), 2-methylbut-3-yn-2-ol (0.200 ml, 2 mmol), [$PdCl_2(PPh_3)_2$] (70 mg, 0.1 mmol), CuI (19 mg, 0.1 mmol), and Et_3N (0.28 ml, 2 mmol) in DMF (2 ml) was heated at 60° under N_2 for 1 h. The mixture was then diluted in H_2O and extracted with AcOEt, the org. layer washed twice with 2% aq. HCl soln. and twice with sat. NaCl soln., dried ($MgSO_4$), and evaporated, and the residual brown oil submitted to CC (silica gel, hexane/

AcOEt 1:1): **10** (140 mg, 72%). Brown oil. FT-IR: 3407 (OH), 2981, 2935, 2832, 1699,, 1649, 1585, 1462, 1376, 1324, 1271, 1237, 1205, 1156, 1072, 1036, 1009, 982, 956, 925, 878. ^{1}H-NMR ($CDCl_3$): 10.40 (*s*, CHO); 7.29 (*s*, H−C(4)); 5.17 (*s*, CH_2); 5.16 (*s*, CH_2); 3.56 (*s*, Me); 3.50 (*s*, Me); 2.86 (*s*, OH); 1.62 (*s*, Me); 1.60 (*s*, Me). ^{13}C-NMR ($CDCl_3$): 190.01 (CHO); 154.29; 154.21; 130.95; 124.43 (C(4)); 118.56; 115.50; 106.35; 100.85; 100.59 (CH_2); 99.65; 95.48 (CH_2); 74.95; 65.48; 58.09 (MeO); 56.43 (MeO); 31.13 (2 Me); 31.09 (2 Me).

6-(3-Hydroxy-3-methylbut-1-ynyl)-2-(1-hydroxy-1-methylethyl)-5-(methoxymethoxy)benzofuran-7-carboxaldehyde (**11**) was obtained as major product under the conditions described for **10**, but at higher temp. Yield: 60%. FT-IR: 3449 (OH), 2981, 2934, 1690, 1645, 1607, 1450, 1369, 1261, 1224, 1205, 1153, 1118, 1072, 1046, 1015, 998, 969, 934, 848. ^{1}H-NMR ($CDCl_3$): 10.61 (*s*, CHO); 7.46 (*s*, H−C(4)); 6.53 (*s*, H−C(3)); 5.24 (*s*, CH_2); 3.56 (*s*, MeO); 1.69 (*s*, 4 Me). ^{13}C-NMR ($CDCl_3$): 190.66 (CO); 167.18; 154.03; 147.58; 130.53; 120.93; 114.04 (C(4)); 105.34; 99.86 (C(3)); 96.13 (CH_2); 74.52; 68.64; 65.77; 60.39; 56.37; 31.19 (2 Me); 28.35 (2 Me).

2,5-Dihydroxy-3,6-bis(3-methylbut-3-en-1-ynyl)benzaldehyde (**1**). A soln. of **10** (223 mg, 0.57 mmol) in toluene (5 ml) was stirred at 60° for 5 h in the presence of a catalytic amount of TsOH. The soln. was diluted with AcOEt, washed with sat. NaCl soln., dried ($MgSO_4$), and evaporated, and the residue purified by CC (silica gel, AcOEt/hexane 1:4): **1** (25 mg, 25%). ^{1}H-NMR ($CDCl_3$): 11.70 (*s*, OH); 10.30 (*s*, CHO); 7.27 (*s*, arom. H); 5.42 (*m*, OH, 2 CH_2); 2.06 (*t*, Me); 2.02 (*t*, Me). ^{13}C-NMR ($CDCl_3$): 196.47 (CHO); 157.84, 150.22 (C(2), C(5)); 127.17 (C(4)); 126.08; 125.52 (CH_2); 124.01 (CH_2); 118.40; 115.43; 111.61; 105.91; 98.71; 82.91; 23.95 (Me); 23.86 (Me).

3-(Hydroxymethyl)-2,5-bis(3-methylbut-3-en-1-ynyl)benzene-1,4-diol (**2**). A soln. of **1** (7 mg, 0.03 mmol) in MeOH (5 ml) was cooled at −70°, and excess of $NaBH_4$ was added portionwise. After 10 min, the yellow color disappeared, and the soln. was diluted with H_2O/10% HCl soln. 5:1. The resulting soln. was extracted with AcOEt (3 × 10 ml), the extract washed with NaCl, dried ($MgSO_4$), and evaporated, and the residue purified by CC (silica gel, hexane/AcOEt 4:1): **2** (6 mg, 86%). White solid. ^{1}H-NMR ($CDCl_3$): 6.91 (*s*, arom. H); 6.32 (*s*, OH−C(arom.)); 5.41 (*m*, CH_2); 5.31 (*m*, CH_2); 4.91 (*d*, CH_2OH); 2.41 (*t*, CH_2O*H*); 2.01 (*m*, 2 Me). ^{13}C-NMR ($CDCl_3$): 149.70; 148.98; 126.31; 126.03; 125.75; 123.63 (CH_2); 123.31 (CH_2); 116.30 (C(6)); 111.74; 110.26; 102.75; 98.49; 82.06; 79.83; 60.66 (CH_2OH); 23.28 (2 Me). EI-MS: 268 (54, M^+), 250 (100), 235 (7), 221 (7), 207 (8), 193 (6), 179 (25), 178 (32).

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